Notes

(±)-(Z)-2-(Aminomethyl)-1-phenylcyclopropanecarboxamide Derivatives as a New Prototype of NMDA Receptor Antagonists

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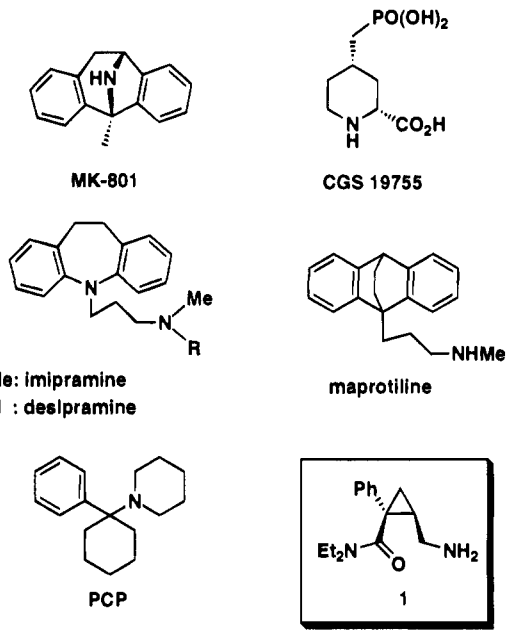
(±)-(*Z*)-2-(Aminomethyl)-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide (milnacipran, **1**), a clinically useful antidepressant, and its derivatives were prepared by an improved method and were evaluated as NMDA receptor antagonists. Of these, milnacipran (**1**), its *N*-methyl and *N*,*N*-dimethyl derivatives, **7** and **8**, respectively, and its homologue **12** at the aminomethyl moiety had binding affinity for the receptor *in vitro* (IC_{50}: **1**, 6.3 ± 0.3 μM; **7**, 13 ± 2.1 μM; **8**, 88 ± 1.4 μM; **12**, 10 ± 1.2 μM). These also protected mice from NMDA-induced lethality. These compounds would be important as anovel prototype for designing potent NMDA-receptor antagonists because of their characteristic structure, which clearly differentiated them from known competitive and noncompetitive antagonists to the receptor.

Introduction

Activation of the *N*-methyl-D-aspartate (NMDA) receptor, a subclass of glutamate receptors, is involved in a variety of cognitive and neurodegenerative processes,[1] and there is pharmacological evidence for the therapeutic potential of NMDA receptor antagonists.[2,3] For instance, MK-801 [10,11-dihydro-5-methyl-5*H*-dibenzo[*a*,*b*]cyclohepten-5,10-imine][2] and CGS 19755 [(±)*cis*-4-(phosphonomethyl)-2-piperidinecarboxylic acid],[3] which are noncompetitive and competitive NMDA receptor antagonists, respectively, are effective in experimental models of epilepsy and stroke. The noncompetitive inhibitors had serious behavior effects[4a,b] probably due to neuronal vacuolization,[4c] while the competitive ones were often inactive in vivo because of poor transport to the brain.[5] Therefore, development of another type of NMDA receptor antagonists has been needed.

Various antidepressants with tri- or tetracyclic backbone structures, such as imipramine, desipramine, and maprotiline, have also been reported to bind to the NMDA receptor.[6] (±)-(*Z*)-2-(Aminomethyl)-1-phenylcyclopropane-*N*,*N*-diethylcarboxamide (milnacipran, **1**)[7] is a member of a new class of potent antidepressants.[8] Milnacipran inhibits the reuptake of serotonin (5-HT) and noradrenalin by the nerve terminal in CNS.[8] On the other hand, studies on its binding to a wide range of receptors and binding sites showed a total lack of affinity of it for any neurotransmitter receptors,[8] so it is free of anticholinergic effects[8] which are often observed in treatment with the usual antidepressants. This desirable feature of **1** could be due to its cyclopropane backbone structure, which is very different from the tri- or tetracyclic structure of other antidepressants. Because study of **1** on NMDA receptor has not been reported, we were interested in investigating whether

Chart 1



1 and its derivatives act as antagonists to the NMDA receptor, as observed in investigating whether **1** and its derivatives act as antagonists to the NMDA receptor, as observed in tri- or tetracyclic antidepressants. These compounds could be an important prototype for developing useful NMDA receptor antagonists that would be free from serious side effects and could be readily transported to the brain.

On the basis of these considerations, first, we synthesized milnacipran (**1**) by a new convenient synthetic procedure and then found **1** to bind to the NMDA receptor *in vitro*. We next prepared a variety of its derivatives and evaluated their effects on the NMDA receptor in order to investigate the structure–activity relationships.

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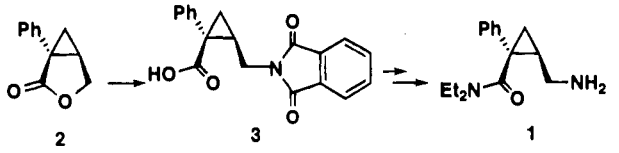
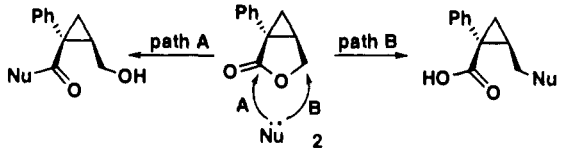
Scheme 1



Scheme 2



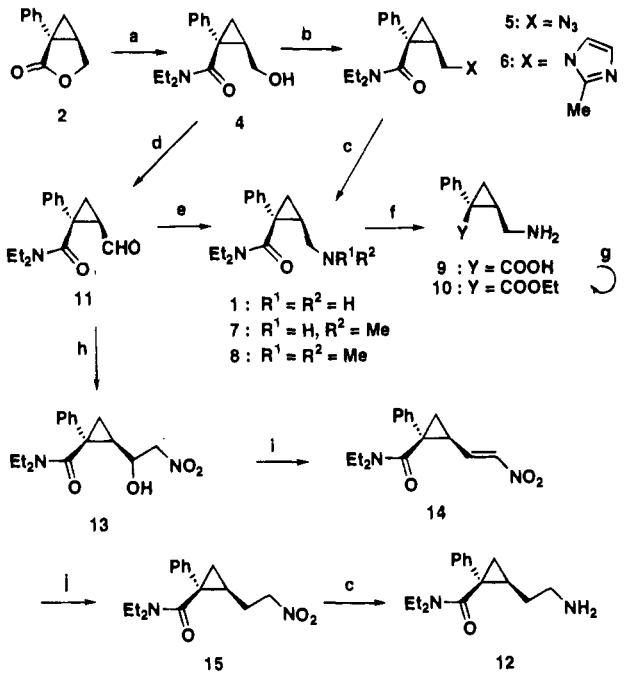
Chemistry

Milnaciprin (**1**) has been synthesized from lactone **2**, as a key intermediate.[9] In this method, **2** was treated with potassium phthalimide in DMSO giving a ring-opening product **3** in 57% yield, which was converted to **1** in several reaction steps (Scheme 1). However, the overall yield was not high enough and the method seemed unsuitable for preparing various derivatives of **1**, especially for derivatives modified at the 2-aminomethyl moiety. Therefore, we developed an alternative method for synthesizing **1** and its derivatives from **2**, which was readily prepared from epichlorohydrin and phenylacetonitrile by a reported method[10] with a slight modification. It was thought that the lactone **2** could react with nucleophiles at two sites in the molecule, namely, through paths A and B (Scheme 2). We attempted to open the lactone ring of **2** at the carbonyl carbon (path A) by a nucleophilic substitution reaction with nitrogen nucleophiles, not at the α-methylene carbon of the cyclopropane ring as previously reported (path B).[9] The desired ring opening at the carbonyl position did not happen upon heating with an excess of Et_2NH in MeOH or in DMF. However, when **2** was treated with lithium diethylamide, prepared from Et_2NH and BuLi at −78 °C, the desired substitution reaction occurred at the carbonyl carbon to give *N,N*-diethylcarboxamide **4** quantitatively (Scheme 3). Compound **4** was converted to an azide derivative, **5**, in 96% yield by treating it with a $LiN_3/CBr_4/Ph_3P$ system in DMF. Catalytic hydrogenation of **5** with Pd−C in MeOH gave milnaciprin (**1**) in 91% yield. In this procedure, **1** was readily obtained in 87% overall yield from **2**, which surpassed the previous method.

We also synthesized derivatives of **1** modified in the aminomethyl or carboxamide moiety to investigate the structure−activity relationships. Compound **1** was treated with aqueous HCl to afford amino acid **9**, which was converted to the corresponding ethyl ester **10**. The ring-opening product **4** was a good intermediate for synthesizing various derivatives of **1** modified in the aminomethyl moiety. Swern oxidation of **4** gave the aldehyde **11** in 91% yield, which was reductively aminated with $NaBH_3CN$ and $MeNH_2$, or Me_2NH in MeOH gave the corresponding *N*-methylamino and *N,N*-dimethylamino derivatives **7** and **8**, respectively. The 2-methylimidazole derivative **6** was also prepared directly from **4** by treating it with 2-methylimidazole in the presence of CBr_4 and Ph_3P in DMF.

We next synthesized a homologue of milnaciprin, **12**, at the aminomethyl moiety, to investigate the influence on the biological effects, when the distance between the

Scheme 3[a]



[a] Conditions: (a) Et_2NH, BuLi, THF, −78 °C; (b) CBr_4, PPh_3, LiN_3 or 2-methylimidazole, DMF, room temperature; (c) 10% Pd−C, H_2, MeOH, room temperature; (d) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, −78 °C; (e) $NaBH_4CN$, NH_2Me·HCl or $NHMe_2$·HCl, MeOH, room temperature; (f) 5 N HCl, reflux; (g) HCl, EtOH, reflux; (h) CH_3NO_2, NaH, THF, room temperature; (i) MsCl, Et_3N, CH_2Cl_2, room temperature; (j) $NaBH_4$, EtOH, room temperature.

biologically important basic amino group and other functional groups in the molecule was changed. The homologue **12** was prepared via a nitro−aldol reaction. Reaction of aldehyde **11** and CH_3NO_2 in the presence of NaH in THF afforded an addition product, **13**, as a single diastereomer in high yield. Treatment of **13** under the usual mesylation conditions ($MsCl/Et_3N/CH_2Cl_2$) directly gave the corresponding elimination product **14** in 75% yield as crystals.[11] The configuration of the olefin moiety of **14** was assigned as *E* from its ^1H NMR spectrum. Compound **14** was reduced with $NaBH_4$ in EtOH to give a saturated compound, **15**, in 80% yield. Finally, the nitro group of **15** was reduced by catalytic hydrogenation with Pd−C gave the desired homologue **12** in 65% yield.

Biological Activity

First, milnacipran (**1**) was evaluated *in vitro* for its binding affinity for the NMDA receptor of cerebral cortical synaptic membrane from rats with [^3H]MK-801 as a radioligand.[12] Imipramine, a most useful antidepressant, and an antagonist to the NMDA receptor, was evaluated as a positive control in the same system. The results are shown in Table 1. Compound **1** had an obvious inhibitory effect (IC_{50} = 6.3 ± 0.3 μM) on binding of [^3H]MK-801. The effect was greater than that of imipramine. We decided to prepare various derivatives of **1** and to investigate the structural requirements for affinity for the NMDA receptor.

The binding affinity of these derivatives was evaluated on the NMDA receptor in the same *in vitro* system described above, and the result are also summarized in Table 1. The *N*-methyl and *N,N*-dimethyl derivatives, **7** and **8**, respectively, showed binding activity, but

Table 1. Effects on NMDA Receptor *in Vitro* and *in Vivo*

compound	IC_{50} (μM)[a] [^{3}H]MK-801	NMDA lethality (protection, %)[b] 20 mg/kg	40 mg/kg
1	6.3 ± 0.3	60	100
4	>100	–[c]	–
5	>100	–	–
6	>100	–	–
7	13 ± 2.1	20	30
8	88 ± 1.4	10	40
9	>100	–	–
10	>100	–	–
11	>100	–	–
12	10 ± 1.2	30	20
imipramine	14 ± 0.7	30[d]	70[e]

[a] Binding assay was done with cerebral cortical synaptic membrane of rat in the presence of [^{3}H]MK-801 (4 nM), glutamate (10 μM), and glycine (10 μM). [b] Compounds were administered ip 60 min before iv administration of NMDA in the lethal dose of 90 mg/kg in mice. [c] Not tested. [d] 10 mg/kg. [e] 30 mg/kg.

N-methylation at the amino function reduced the activities of the compounds: **1** (primary amino) > **7** (secondary amino) > **8** (tertiary amino). Methylimidazole derivative **6** was synthesized because the 2-methylimidazole group is known as an efficient bioisostere for a basic amino group[13] but was inactive (IC_{50} > 100 μM). Compounds **9** and **10**, in which the carboxamide moiety was replaced by a carboxyl or ethoxycarbonyl group, respectively, had no activity. All other derivatives lacking a basic amino function were also inactive in this binding assay system. On the other hand, the homologue **12** had an affinity for the receptor (IC_{50} = 10 ± 1.2 μM) somewhat weaker than that of **1**.

The compounds that were active in this *in vitro* evaluation system were nest investigated for protecting against NMDA-induced lethality in mice. The results are also summarized in Table 1. Compounds were administered ip 60 min before treating the mice with a lethal dose of NMDA. All of the compounds tested protected the mice from death at least to some degree. Milnaciprin (**1**) showed the best activity; treatment of 40 mg/kg of **1** completely inhibited the lethality of NMDA. Thus, the *in vivo* results were correlated with the above *in vitro* binding affinity for the receptor.

These biological results and the structural features of the compounds, lacking an acidic function indispensable for the competitive antagonists to the NMDA receptor, suggested that these functioned as antagonists to the receptor in an uncompetitive manner. These results also disclosed that the presence of both an amino and a carboxamide function in these phenylcyclopropane derivatives was essential for their binding to the receptor. From this structural requirement for the activity, the compounds of this study would not belong to the family of known uncompetitive NMDA receptor antagonists, because they generally have an analogous structural feature, typified by those of MK-801 and PCP [1-(1-phenylcyclohex-1-yl)piperidine]. Consequently, the compounds in this study may be free from the serious side effects observed in the known uncompetitive antagonists.[4]

In conclusion, we developed a new efficient method for synthesizing milnacipran as well as its derivatives and showed them to be a new class of NMDA receptor antagonists. Although milnacipran is a strong inhibitor of monoamine reuptake (5-HT, IC_{50} = 203 nM; noradrenalin, IC_{50} = 100 nM)[8b] and the binding affinities of the compounds for the NMDA receptor *in vitro* may not be strong enough, these showed significant protection against NMDA-induced lethality in mice. Therefore, these have vital importance as a prototype for designing novel potent NMDA-receptor antagonists because of the characteristic structure which is clearly different from those of known competitive and noncompetitive antagonists to the receptor. Further modification studies of milnacipran, increasing the specific affinity of compounds for the NMDA receptor, would be required to develop a clinically useful NMDA receptor antagonist.

Experimental Section

Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The NMR spectra were recorded with a JEOL EX-270 or GSX-400 or a Bruker ARX-500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by the addition of D_2O. Mass spectra were measured on a JEOL JMS-D300 spectrometer. Thin-layer chromatography was done on Merck coated plates $60F_{254}$. Silica gel chromatography and flash silica gel chromatography were done with Merck silica gel 5715 and 9385, respectively.

(±)-(*Z*)-2-Oxo-1-phenyl-3-oxabicyclo[3.1.0]hexane (2). Compound **2** was prepared by modification of the previously reported procedure.[10] A solution of phenylacetonitrile (11.5 mL, 100 mmol) in benzene (20 mL) was added slowly to a suspension of $NaNH_2$ (8.58 g, 220 mmol) in benzene (40 mL) at 0 °C under argon, and the mixture was stirred at room temperature for 3 h. To the resulting mixture was added a solution of (±)-epichlorohydrine (6.8 mL, 87 mmol) in benzene (20 mL) at 0 °C, and the whole was stirred at room temperature for 2 h. After the solvent was evaporated, EtOH (20 mL) and 1 N KOH (10 mL) were added to the residue, and the mixture was heated under reflux for 15 h and then acidified with 12 N HCl at 0 °C (pH of the mixture was about 1). The resulting mixture was evaporated, and AcOEt (300 mL) was added to the residue. Insoluble salts were filtered off, and the filtrate was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:3) to give **2** (10.1 g, 58% as an oil): FAB-MS *m/z* 193 (MH^+); ^{1}H-NMR (100 MHz, $CDCl_3$) 1.35 (1 H, dd, H-6a, *J* = 4.6 and 4.9 Hz), 1.64 (1 H, dd, H-6b, *J* = 4.9 and 7.7 Hz), 2.55 (1 H, ddd, H-5, *J* = 4.4, 4.6, and 7.7 Hz), 4.27 (1 H, d, H-4a, *J* = 9.0 Hz), 4.47 (1 H, dd, H-4b, *J* = 4.4 and 9.0 Hz), 7.34 (5 H, m, phenyl).

(±)-(*Z*)-1-Phenyl-2-(hydroxymethyl)cyclopropane-*N*,*N*-diethylcarboxamide (4). To a solution of Et_2NH (63 mL, 600 mmol) in THF (200 mL) was added BuLi (1.55 M in hexane, 390 mL, 600 mmol) slowly at 0 °C under argon, and then the mixture was cooled to −78 °C. To the resulting cooled mixture was added slowly a solution of **2** (35.4 g, 200 mmol) in THF (200 mL), and the whole was stirred at the same temperature. After 2 h, the reaction was quenched with aqueous saturated NH_4Cl (50 mL), the resulting mixture was concentrated *in vacuo* (for removing THF), and then AcOEt (500 mL) was added. The separated organic phase was dried (Na_2SO_4), evaporated, and purified by flash column chromatography (silica gel; AcOEt/hexane, 3:7) to give **4** (49.1 g, 98% as an oil): FAB-MS *m/z* 248 (MH^+); ^{1}H-NMR (400 MHz, $CDCl_3$) 0.91 (3 H, t, CH_2CH_3, *J* = 7.3 Hz), 1.08 (1 H, dd, H-3a, *J* = 4.9 and 6.3 Hz), 1.14 (3 H, t, CH_2CH_3, *J* = 7.3 Hz), 1.55 (1 H, m, H-2), 1.65 (1 H, dd, H-3b, *J* = 4.9 and 8.8 Hz), 3.17 (1 H, ddd, CH_2O, *J* = 2.4, 10.3, and 12.2 Hz), 3.32−3.56 (4 H, m, 2 × CH_2CH_3), 4.40 (1 H, ddd, CH_2O, *J* = 4.9, 11.2, and 12.2 Hz), 4.74 (1 H, dd, OH, *J* = 2.4 Hz and 11.2 Hz), 7.19−7.32 (5 H, m, phenyl). Anal. ($C_{15}H_{19}NO_2 \cdot 0.1H_2O$) C, H, N.

(±)-(*Z*)-1-Phenyl-2-(azidomethyl)cyclopropane-*N*,*N*-diethylcarboxamide (5). A mixture of Ph_3P (8.6 g, 36 mmol), CBr_4 (12 g, 36 mmol), and **4** (2.89 g, 12.0 mmol) in DMF (60 mL) was stirred at room temperature. After 1 h, NaN_3 (7.95

g, 12 mmol) was added at 0 °C, and the whole was stirred at room temperature for 5 h. Brine (30 mL) and AcOEt (300 mL) were added to the resulting mixture. The organic phase was separated, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography (silica gel; AcOEt/hexane, 1:20) to give **5** (3.12 g, 96% as an oil): EI-MS *m/z* 272 (M^+); ^{1}H-NMR (270 MHz, $CDCl_3$) 0.56 (3 H, t, CH_2CH_3, J = 7.0 Hz), 1.11 (3 H, t, CH_2CH_3, J = 6.9 Hz), 1.18 (1 H, dd, H-3a, J = 5.0 and 8.9 Hz), 1.57 (1 H, dd, H-3b, J = 5.0 and 5.2 Hz), 1.98 (1H, m, H-2), 3.03–3.33 (2H, m, CH_2CH_3), 3.38 (2 H, d, CH_2N_3, J = 5.4 Hz), 3.41–3.66 (1 H, m, CH_2CH_3), 7.19–7.34 (5 H, m, phenyl). Anal. ($C_{15}H_{21}N_4O\cdot0.1H_2O$) C, H, N.

(±)-(Z)-1-Phenyl-2-(aminomethyl)cyclopropane-*N,N*-diethylcarboxamide Hydrochloride (milnacipran, 1). A mixture of **5** (272 mg, 1 mmol) and 10% Pd–charcoal (27 mg) in MeOH (8 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 1.5 h, and then the catalyst was filtered off. The filtrate was evaporated, and the residue was partitioned between $CHCl_3$ and 1 N NaOH. The $CHCl_3$ phase was washed twice with H_2O, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (3 mL), the solution was put on a column of Diaion WA-30 resin (Cl^- form), and the column was developed with MeOH. The eluate was evaporated. The residue was treated with benzene to give 1 (hydrochloride, 258 mg, 91% as white crystals): mp 174–175 °C (lit.[9] mp 179–181 °C); FAB-MS *m/z* 247 (MH^+); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.90 (3 H, t, CH_2CH_3, J = 7.1 Hz), 1.11–1.15 (4 H, m, H-3a and CH_2CH_3), 1.74 (1H, m, H-2), 1.86 (1 H, dd, H-3b, J = 5.7 and 8.9 Hz), 2.47 (1 H, dd, CH_2NH_2, J = 13.1 and 13.5 Hz), 3.47–3.25 (4H, m, CH_2CH_3 × 2), 3.76 (1 H, dd, CH_2NH_2, J = 13.1 and 4.6 Hz), 7.17–7.30 (5 H, m, phenyl). Anal. ($C_{15}H_{22}N_2O\cdot HCl$) C, H, N.

(Z)-1-Phenyl-2-[(2-methylimidazolyl)methyl]cyclopropane-*N,N*-diethylcarboxamide (6). Compound **6** was prepared as described above for **5**, with 2-methylimidazole instead of sodium azide. After purification by flash column chromatography (silica gel; AcOEt/hexane, 1:1), white crystals were obtained from ether–hexane (67% yield): mp 82–84 °C; FAB-MS *m/z* 312 (M^+); ^{1}H-NMR (270 MHz, $CDCl_3$) 0.61 (3 H, t, CH_2CH_3, J = 6.9 Hz), 1.15 (3 H, t, CH_2CH_3, J = 7.2 Hz), 1.34 (1 H, dd, H-3a, J = 5.3 and 9.0 Hz), 1.54 (1 H, dd, H-3b, J = 5.3 and 6.3 Hz), 1.93 (1H, m, H-2), 2.40 (3 H, s, imidazole Me), 2.96–3.09 (1 H, m, CH_2CH_3), 3.31–3.48 (3 H, m, CH_2CH_3), 3.65 (1 H, dd, J = 8.9 and 14.5 Hz), 4.29 (1 H, dd, J = 5.2 and 14.5 Hz), 6.92, 6.98 (each 1 H, each s, imidazole CH), 7.19–7.35 (5 H, m, phenyl). Anal. ($C_{19}H_{25}N_3O$) C, H, N.

(±)-(Z)-1-Phenyl-2-formylcyclopropane-*N,N*-diethylcarboxamide (11). To a solution of oxalyl chloride (0.55 mL, 6.4 mmol) in CH_2Cl_2 (4 mL) was added slowly a mixture of DMSO (0.91 mL, 13 mmol) and CH_2Cl_2 (4 mL) at −78 °C for 30 min under argon. To the resulting mixture was added slowly a solution of **4** (805 mg, 3.26 mmol) in CH_2Cl_2 (4 mL), the whole was stirred at the same temperature for 2 h, and then Et_3N (1.9 mL, 26 mmol) was added. After being stirred at −78 °C for 1 h more, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), and then $CHCl_3$ (10 mL) was added. The organic layer was separated, washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:2) to give **11** (791 mg, 99% as white crystals): mp 61–63 °C (recrystallized from ether); FAB-MS *m/z* 246 (MH^+); ^{1}H-NMR (270 MHz, $CDCl_3$) 0.69 (3 H, t, CH_2CH_3, J = 7.1 Hz), 1.11 (3 H, t, CH_2CH_3, J = 7.1 Hz), 1.71 (1 H, dd, H-3a, J = 5.5 and 8.5 Hz), 2.28 (1 H, dd, H-3b, J = 5.5 and 6.0 Hz), 2.50 (1 H, ddd, H-2, J = 6.0, 6.0 and 8.5 Hz), 3.12–3.52 (4H, m, CH_2CH_3), 7.23–7.38 (5 H, m, phenyl), 9.05 (1 H, d, CHO, J = 6.0 Hz). Anal. ($C_{15}H_{19}NO_2$) C, H, N.

(±)-(Z)-1-Phenyl-2-[(*N*-methylamino)methyl]cyclopropane-*N,N*-diethylcarboxamide Hydrochloride (7). To a mixture of 11 (615 mg, 2.5 mmol) and methylamine hydrochloride (470 mg, 7.0 mmol) in MeOH (25 mL) and THF (25 mL) was added $NaBH_4CN$ (146 mg, 1.23 mmol), and the whole was stirred at room temperature. Methylamine hydrochloride (470 mg, 7.0 mmol) and $NaBH_4CN$ (146 mg, 1.23 mmol) were added after 6 and 14 h, respectively, and then the resulting mixture was stirred for 10 h more. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ and 0.5 N NaOH. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 100:10:1). The fractions containing the desired product were evaporated, and the residue was partitioned between $CHCl_3$ and 1 N NaOH. The $CHCl_3$ phase was washed twice with H_2O and evaporated. The residue was dissolved in MeOH (3 mL), the solution was put on a column of Diaion WA-30 resin (Cl^- form), and the column was developed with MeOH. The eluate was evaporated, and the residue was treated with Et_2O to give **7** (189 mg, 27% as white crystals): mp 201–202 °C; FAB-MS *m/z* 261 (MH^+); ^{1}H-NMR (270 MHz, $CDCl_3$ + D_2O) 0.91 (3 H, t, CH_2CH_3, J = 7.2 Hz), 1.15 (3 H, t, CH_2CH_3, J = 7.2 Hz), 1.17 (1 H, dd, H-3a, J = 5.9 and 9.2 Hz), 1.78 (1 H, m, H-2), 1.98 (1H, dd, H-3b, J = 5.9 and 9.2 Hz), 2.48 (1 H, dd, CH_2-NHMe, J = 11.2 and 12.6 Hz), 3.23–3.50 (4 H, m, 2 × CH_2-CH_3), 3.71 (1 H, dd, J = 5.1 and 12.9 Hz), 7.17–7.38 (5 H, m, phenyl). Anal. ($C_{16}H_{24}N_2O\cdot HCl\cdot0.5H_2O$) C, H, N.

(±)-(Z)-1-Phenyl-2-[(*N,N*-dimethylamino)methyl]cyclopropane-*N,N*-diethylcarboxamide Hydrochloride (8). Compound **8** was prepared as described above for **7** in 51% yield, with dimethylamine hydrochloride instead of methylamine hydrochloride: mp 202–205 °C; FAB-MS *m/z* 275 (MH^+); ^{1}H-NMR (270 MHz, $CDCl_3$, D_2O added) 0.75 (3 H, t, CH_2CH_3, J = 7.2 Hz), 1.14 (3 H, t, CH_2CH_3, J = 7.2 Hz), 1.50 (1 H, dd, H-3a, J = 5.4 and 10.8 Hz), 1.75–1.90 (2 H, m, H-2 and H-3b), 3.13 (1 H, dd, CH_2NHMe, J = 7.8 and 13.0 Hz), 3.20–3.50 (4 H, m, 2 × CH_2CH_3), 3.71 (1 H, dd, CH_2NHMe, J = 5.4 and 13.0 Hz), 7.20–7.38 (5 H, m, phenyl). Anal. ($C_{17}H_{26}N_2O\cdot HCl\cdot0.5H_2O$) C, H, N.

(±)-(Z)-1-Phenyl-2-(aminomethyl)cyclopropanecarboxylic Acid Hydrochloride (9). A solution of 1 (282 mg, 1.0 mmol) in 5 N HCl (5 mL) was heated under reflux for 16 h, and then the solvent was evaporated. The residue was treated with MeOH to give **9** (189 mg, 83% as colorless crystals): mp >220 °C; FAB-MS *m/z* 192 (MH^+); ^{1}H-NMR (270 MHz, DMSO-d_6) 1.49 (1 H, dd, H-3a, J = 4.6 and 9.2 Hz), 1.61 (1 H, dd, H-3b, J = 4.6 and 6.9 Hz), 1.88 (1 H, m, H-2), 3.12 (1 H, m, CH_2N), 3.34 (1 H, m, CH_2N), 7.29–7.48 (5 H, m, phenyl). Anal. ($C_{11}H_{13}NO_2\cdot HCl$) C, H, N.

Ethyl (±)-(Z)-1-Phenyl-2-(aminomethyl)cyclopropanecarboxylate Hydrochloride (10). To a solution of **9** (400 mg, 1.76 mmol) in EtOH (10 mL) was added 12 N HCl (150 μL) and the mixture was heated under reflux for 16 h. The solvent was evaporated, and the residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 20:1) to give **10** (220 mg, 49% as a white foam): EI-MS *m/z* 219 (M^+); ^{1}H-NMR (270 MHz, $CDCl_3$) 1.17 (3 H, t, CH_2CH_3, J = 7.3 Hz), 1.29 (1 H, dd, H-3a, J = 4.6 and 8.5 Hz), 1.60 (1 H, dd, H-3b, J = 4.6 and 7.3 Hz), 1.69 (1 H, m, H-2), 2.85 (1 H, dd, CH_2N, J = 8.3 and 13.5 Hz), 3.02 (1 H, dd, CH_2N, J = 6.2 and 13.5 Hz), 4.04–4.18 (2 H, m, CH_2CH_3), 7.21–7.44 (5 H, m, phenyl). Anal. ($C_{13}H_{17}NO_2\cdot HCl\cdot H_2O$) C, H, N.

(±)-(Z)-1-Phenyl-2-(1-hydroxy-2-nitroethyl)cyclopropane-*N,N*-diethylcarboxamide (13). To a mixture of NaH (55%, 22 mg, 0.5 mmol) and CH_3NO_2 (220 mg, 0.4 mmol) in THF (5 mL) was added 11 (100 mg, 0.41 mmol) at 0 °C, the whole was stirred at room temperature for 1 h, and then saturated NH_4Cl (3 mL) was added. The resulting mixture was concentrated and extracted with AcOEt (15 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography (silica gel; AcOEt/hexane, 1:5). The fractions containing the desired product were concentrated to give **13** (100 mg, 80% as needles): mp 133–134 °C; EI-MS *m/z* 306 (M^+); ^{1}H-NMR (270 MHz, $CDCl_3$) 0.91 (3 H, t, CH_2CH_3, J = 6.9 Hz), 1.15 (3 H, t, CH_2CH_3, J = 6.9 Hz), 1.15 (1 H, m, H-3a), 1.29 (1 H, m, H-2), 1.78 (1 H, dd, H-3b, J = 5.6 and 8.2 Hz), 3.30–3.54 (4 H, m, 2 × CH_2CH_3), 3.94 (1 H, m, CHOH), 4.49 (1 H, dd, CH_2NO_2, J = 5.3 and 11.8 Hz), 4.6 C4 (1 H, dd, CH_2-NO_2, J = 7.9 and 11.8 Hz), 5.76 (1 H, br, OH), 7.21–7.35 (5 H, m, phenyl). Anal. ($C_{16}H_{22}N_2O_4$) C, H, N.

(±)-(Z)-1-Phenyl-2-(2-nitroethenyl)cyclopropane-*N,N*-diethylcarboxamide (14). To a solution of **13** (900 mg, 2.9 mmol) and Et_3N (1.2 mL, 9.0 mmol) in CH_2Cl_2 (10 mL) was added MsCl (0.34 mL, 4.5 mmol) at 0 °C, the mixture was stirred at room temperature for 1 h, and then aqueous saturated NH_4Cl (5 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (silica gel; AcOEt/hexane, 1:9). The fractions containing the desired product were concentrated to give **14** (650 mg, 75% as yellowcrystals): mp 131–132 °C; EI-MS *m/z* 288 (M^+); ^{1}H-NMR (500 MHz, $CDCl_3$) 0.62 (3 H, t, CH_2CH_3, J = 7.0 Hz), 1.1 (3 H, t, CH_2CH_3, J = 7.0 Hz), 1.64 (1 H, dd, H-3a, J = 5.5 and 8.5 Hz), 1.99 (1 H, dd, H-3b, J = 5.5 and 6.0 Hz), 2.49 (1 H, ddd, H-2, J = 6.0, 8.5, and 11.0 Hz), 3.01–3.19 (2 H, m, CH_2CH_3), 3.34–3.61 (2 H, m, CH_2CH_3), 6.98 (1H, dd, CH=, J = 11.0 and 13.0 Hz), 7.21 (1 H, d, CH=, J = 13.0 Hz), 7.22–7.37 (6 H, m, phenyl). Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

(±)-(Z)-1-Phenyl-2-(2-nitroethyl)cyclopropane-*N,N*-diethylcarboxamide (15). To a solution of **14** (460 mg, 1.6 mmol) in EtOH (30 mL) was added $NaBH_4$ (300 mg, 8.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h and then neutralized with 1 N HCl. The resulting mixture was evaporated, and the residue was partitioned between AcOEt and brine. The separated organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography (silica gel; AcOEt/hexane, 1:2) to give **15** (370 mg, 80% as an oil): FAB-MS *m/z* 291 (MH^+); ^{1}H-NMR (270 MHz, $CDCl_3$) 0.66 (3 H, t, CH_2CH_3, J = 7.0 Hz), 1.12 (3 H, t, CH_2CH_3, J = 7.0 Hz), 1.21 (1 H, dd, H3a, J = 5.3 and 8.5 Hz), 1.35 (1 H, dd, H-3b, J = 5.3 and 5.9 Hz), 1.66 (1 H, m, H-2), 1.85 (1 H, m, $CH_2CH_2NO_2$), 2.35 (1 H, m, $CH_2CH_2NO_2$), 3.08–3.30 (2 H, m, CH_2CH_3), 3.42–3.59 (2 H, m, CH_2CH_3), 4.53–4.70 (2 H, m, $CH_2CH_2NO_2$), 7.16–7.30 (5 H, m, phenyl). This compound was used directly for the next reaction without further purification.

(±)-(Z)-1-Phenyl-2-(2-aminoethyl)cyclopropane-*N,N*-diethylcarboxamide (12). A mixture of **15** (240 mg, 0.83 mmol) and 10% Pd–charcoal (80 mg) in MeOH (5 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 1 h, and then the catalyst was filtered off. The filtrate was evaporated, and the residue was purified by flash column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 100:10:1) to give **12** (140 mg, 65% as a syrup): FAB-MS *m/z* 261 (MH^+); ^{1}H-NMR (270 MHz, $CDCl_3$) 0.56 (3 H, t, CH_2CH_3, J = 7.0 Hz), 0.93 and 1.07 (each m, each 1 H, H-2 and H-3a), 1.11 (3 H, t, CH_2CH_3, J = 7.0 Hz), 1.45 (1 H, dd, H-3b, J = 4.6 and 5.8 Hz), 1.86 (2 H, m, $CH_2CH_2NH_2$), 2.88 (2 H, m, $CH_2CH_2NH_2$), 3.05–3.24 (2 H, m, CH_2CH_3), 3.49–3.64 (2 H, m, CH_2CH_3), 7.16–7.30 (5 H, m, phenyl). Anal. ($C_{16}H_{24}N_2O$) C, H, N.

Binding Study on the NMDA Receptor. Binding affinity on the NMDA receptor *in vitro* was evaluated with cerebral cortical synaptic membranes from rats according to a previously reported method.[12]

Effects on NMDA-Induced Lethality in Mice. Male ddY mice (20–28 g, SLC) in groups of 10 were treated with various doses of test compounds dissolved in saline by the intraperitoneal route. Sixty minutes later, the mice were challenged with a lethal intravenous dose (90 mg/kg) of NMDA dissolved in saline. The test compounds and NMDA were administered in a volume of 100 μL per 10 g of body weight and 50 μL per 10 g of body weight, respectively.

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